REMARKS

Claims 9, 11-17, and 21-58 are pending in the application. Claim 57 is amended. Support for the amendment can be found in the specification at least at page 5, lines 4-7. No new matter has been added.

Applicants thank the Examiner and her supervisor for their time and consideration during the telephonic interview with the undersigned and her colleague, Allyson Hatton, on October 24, 2006 (the "interview"). During the interview, it was agreed that the term "intensity," as it is used in claims 9 and 54, is acceptable and does not render the claims vague or indefinite. It was also agreed that the term "intensity" has written description support in the specification, *e.g.*, at page 2, line 1. A proposed amendment to claim 57 was also found acceptable, and the amended claim, as agreed upon, appears in the amendment above.

As discussed in the telephonic interview, Applicants also respectfully remind the Examiner to consider the references submitted with the supplementary information disclosure statements on January 10, 2006, and November 4, 2005, and return an initialed copy of the Forms PTO-1449. Applicants also repeat their requests in the responses filed November 4, 2005, and December 20, 2004, that the Examiner consider the references cited in the Form PTO-1449 originally submitted with the application on November 13, 2001, and submitted a second time by facsimile on July 19, 2002. Examiner noted on a copy of the Form PTO-1449 returned to Applicants on January 29, 2002, that references AF-AQ were not provided. Applicants have pointed out that reference AF was originally cited by the Examiner in the U.S. priority application 09/194,290 (hereafter, the "'290 application"), filed November 23, 1998, and reference AG was originally submitted by Applicants in the '290 application. Documents AH-AQ were originally submitted by Applicants in U.S. priority application 09/670,457, filed September 26, 2000. Thus, all of the references are of record in this family of cases and presumably available to the Examiner. Applicants therefore request that the Examiner consider these references and return an initialed copy of the Form PTO-1449. New copies of these references will be provided if necessary.

35 U.S.C. § 112, first paragraph

Claims 9, 11-17, 21-40, 54 and 57 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action stated that the term "intensity" in claims 9-54 lacks literal support in the specification as originally filed. Support for "intensity" can be found in the specification at page 2, line 1. The Examiner and her supervisor agreed in the interview that this support was adequate and that the rejection would be withdrawn.

The Office Action also stated that there is no literal support in the specification for the language of claim 57 reciting the amount of formoterol being delivered as being "42 nmol." Claim 57 has been amended to delete the reference to "42 nmol." In the interview, the Examiner and her supervisor informed Applicants' representatives that the proposed amendment to claim 57 was acceptable and rendered the rejection moot.

In view of the foregoing, Applicants respectfully request that the rejection of claims 9, 11-17, 21-40, 54 and 57 under 35 U.S.C. § 112, first paragraph, be withdrawn.

35 U.S.C. § 112, second paragraph

Claims 9, 11-17, 21-40 and 54 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Office Action stated that the term "intensity" is vague and indefinite. As acknowledged by the Examiner and her supervisor in the interview, one having skill in the art would understand from reading the specification, and particularly in view of the context at page 2, lines 1-2, the meaning of "intensity" as it is used in the claims.

35 U.S.C. § 103

The Examiner has maintained the rejection of claims 9, 11-17, and 21-58 under 35 U.S.C. § 103 as being unpatentable over Carling *et al.* (WO 93/11773) in view of Cazzola *et al.* ("Effect of Salmeterol and Formoterol in Patients with Chronic Obstructuve Pulmonary Disease" *Pulmonary Pharmacology* 7:103-107, 1994) and Renkema *et al.* ("Effects of Long-term Treatment with Corticosteroids in COPD" *Chest* 109:1156-1162, 1996) and further in view of Giardina *et al.* (U.S. Patent No. 6,227,862 B1).

The Office Action states that Carling *et al.* "teach a medicament containing effective amounts of formoterol and budesonide in combination for simultaneous, sequential or separate administration by inhalation in treatment of respiratory disorder..." Office Action at page 4. The Examiner concedes that Carling *et al.* does not expressly teach the treatment of COPD. According to the Examiner, Cazzola *et al.* teaches that formoterol is effective in patients with COPD; Renkema teaches that treatment with corticosteroids (*i.e.*, budesonide) significantly reduced pulmonary symptoms in patients with COPD; and Giardina *et al.* reports that COPD and asthma are respiratory disorders. Id. at page 5. The Examiner concludes that it would have been obvious to use Carling's medicament in

> reducing the frequency and/or intensity of COPD since COPD is a well-known respiratory disease as disclosed by Giardina et al., and Giardina et al. teach that the combination is useful for the treatment of respiratory disorders...One of ordinary skill in the art would have been motivated to employ Carling's medicament in reducing the severity or intensity or frequency of having COPD with reasonable expectation of success since each of the active agents utilized in Carling's medicament are well known individually for effectively treating...COPD. Absent any evidence to the contrary, there would have been a reasonable expectation of successfully treating COPD by employing Carling's formulation... Id. at pages 5-6.

As stated in the record, Applicants disagree with the Examiner's characterization of the prior art. In summary, Applicants maintain that Carling *et al.* teaches a combination of budesonide and formoterol for the treatment of asthma, and disorders like asthma, *i.e.*, disorders that are bronchospastic in nature. Carling *et al.* does not teach treatment of COPD. Renkema does not teach that a therapeutic agent containing budesonide will treat exacerbations, and also does not teach use of budesonide at the low concentrations recited in any of the pending claims that recite concentrations of budesonide. Cazzola *et al.* does not teach that formoterol can reduce exacerbations. Giardina teaches quinoline derivatives and their use in medicine, and therefore is not relevant to the present case. The teachings of the prior art provide no guidance that would lead one of ordinary skill in the art to expect that a combination therapy of budesonide and formoterol could be used to treat COPD with any reasonable expectation of success.

In the Reply to Office Action filed November 4, 2005 ("the previous reply"), Applicants traversed the rejection on a number of grounds, including the following:

1. The references do not provide either the motivation or the expectation of success necessary to make out a *prima facie* case of obviousness;

2. The prior art as a whole actually teaches away from the claimed methods;

3. The surprising results observed by Applicants are cogent, objective evidence that the claimed methods cannot be deemed obvious; and

4. Even years after the present application's filing date, experts in the field of respiratory therapy continued to express doubt that budesonide (whether alone or in the claimed combination therapy) would be useful for treating COPD.

The Examiner addresses each of these points in the final Office Action, and Applicants comment on each, in turn, below.

1. Applicants argued that the references do not provide either the motivation or the expectation of success to make out a *prima facie* case of obviousness. The Examiner found this argument unpersuasive, because "Carling *et al.* clearly teach the combination is useful for the treatment of asthma and other respiratory disorder" and Giardina *et al.* refers to COPD and asthma as respiratory diseases. Office Action at page 7. Applicants disagree with this interpretation of Carling.

Applicants have presented a multitude of arguments as to why one of ordinary skill would not read Carling's mention of "respiratory disorders" to encompass COPD. For example, it is not reasonable to read Carling to encompass the treatment of all conditions ever to have been classified as "respiratory disorders." Such an interpretation would mean that Carling teaches treatment of such a wide variety of unrelated disorders, including cough, pulmonary hypertension, lung cancer, and tuberculosis, as well as asthma and COPD. Applicants maintain that Carling should be read to encompass disorders that are <u>like asthma</u>, *i.e.*, bronchospastic in nature. This interpretation is consistent with the evidence in the record.

In the previous reply, Applicants pointed out the distinction between asthma and COPD as reported in the 17th Edition Merck Manual (1999). The Examiner found the argument unpersuasive, citing, *inter alia*, the 16th Edition Merck Manual (1992) ("the 1992 Merck

Manual") as it teaches the interrelationship between COPD and asthma. Applicants believe the Examiner has misinterpreted the teachings of the 1992 Merck Manual, as it actually distinguishes between asthma and COPD by pointing out that the two conditions are quite different and are treated in different ways. For example, at page 65, the 1992 Merck Manual states that **"most asthmatics...have a disease that is almost totally reversible and should not be confused with COPD."** Also at page 65, the 1992 Merck Manual states that **"whenever possible, persons with chronic asthmatic bronchitis should be distinguished from those with a primarily emphysematous type of COPD since the course, prognosis, and response to therapy are distinctly different."** "Asthma" *per se* (as opposed to "chronic asthmatic bronchitis") is addressed under its own heading in a different part of the 1992 Merck Manual (at pages 646-657), so is even more clearly differentiated from COPD. Other teachings in the art before the 1997 priority date of the application also distinguish between asthma and COPD. Renkema (1996), for example, states at page 1156, col. 1: **"The beneficial influence of oral and inhaled corticosteroids is well established in patients with asthma. In contrast, their effectiveness in patients with COPD is controversial, especially during a stable phase of the disease."** Renkema also recognizes the importance for their study of distinguishing COPD patients from asthma patients, stating **"to assess the effectiveness of these drugs in patients with COPD, it is...essential to exclude patients with asthma."** Renkema at page 1160, col. 2. Renkema explains, **"There is general agreement that the inflammatory processes involved in the pathogenesis of the two disease entities are different in nature, and it is not inconceivable that the inflammatory processes in COPD are less sensitive to the anti-inflammatory action of corticosteroids."** Id. at page 1161, col. 2. There is no question that at the filing date of the application, asthma and COPD were recognized as distinct disorders with different causes and different treatments.

2. In the previous reply, Applicants reiterated that the prior art as a whole teaches away from the claimed methods. The Examiner found this argument unpersuasive, stating that Renkema teaches that corticosteroid reduced pulmonary symptoms in patients with COPD, which would motivate one of ordinary skill in the art to use Carling's composition comprising

formoterol (known for treatment of COPD, presumably as taught by Cazzola) and budesonide (as taught by Renkema). Office Action at page 8.

The Examiner is respectfully reminded that claim 9, and the claims depending from claim 9, are directed to a method of reducing the frequency and/or intensity of COPD exacerbations experienced by a patient suffering from COPD. In Renkema's study, **"No significant changes in exacerbation frequency or duration during the study were observed"** in any of the test subjects. Renkema at page 1160, col. 1. The Examiner gives little weight to this observation, stating at page 8 that Renkema's finding of no treatment effect on frequency or duration of exacerbations was "due to high number of withdrawals only." This is not what Renkema says. Renkema actually states only that the observed lack of efficacy **"may have been biased by the pattern of withdrawal."** Renkema at page 1161, col. 1. Renkema's speculation as to a possible problem with the data cannot be taken to be a teaching that the frequency and/or intensity of COPD exacerbations can be reduced by treating a COPD patient with budesonide, either alone or in combination with formoterol. Negative results are negative results, and are not turned into positive results just because the author of the study points out possible weaknesses in the data. The Examiner is also reminded that Cazzola does not teach that formoterol alone can reduce exacerbations in patients with COPD. Thus, since neither Renkema nor Cazzola teaches that either formoterol or budesonide alone can reduce exacerbations in patients with COPD, one of ordinary skill in the art would not read these to suggest that a combination of budesonide and formoterol could reduce the frequency of exacerbations.

Also as pointed out in the previous reply, Renkema tested relatively high doses of budesonide (1600 μg per day) for the treatment COPD over a two-year period. Renkema notes that previous short-term studies had shown budesonide to have **"little or no effect"** (page 1156, col. 1), and reports that, while certain subjective "symptom scores"[1] did decrease during long-term treatment with budesonide alone, neither airflow obstruction (as measured by FEV_1) nor the

[1] The symptom score is described at the top of the second column on page 1157: "Patients were asked to rate the severity of dyspnea (scale, 0 to 5), dyspnea on exertion (scale, 0 to 3), early morning dyspnea (scale, 0 to 3), cough (scale, 0 to 3) and wheeze (scale, 0 to 3). A score of 0 was given if the complaint was absent; a higher value corresponded with increasing severity. A total complaint score (scale, 0 to 17) was calculated by adding up the scores from each question." Dyspnea is difficult or labored breathing. The "symptom score" is thus derived from the patient's own subjective characterization of his difficulty in breathing, rather than on an objectively quantifiable measure such as FEV1 or number of hospitalizations for exacerbations.

frequency or duration of exacerbations was affected by treatment with budesonide (Renkema, p. 1160, column 1). Renkema also states that short-term use of budesonide alone (at any dosage) has no demonstrable benefit in treating COPD. Renkema at page 1156, col. 1. Renkema's long-term trials of budesonide treatment at 1600 μg budesonide per day resulted in what Renkema characterized as "limited" beneficial effect in COPD patients. Renkema at page 1161, col. 2, last paragraph. Renkema's modest results rule out any reason to attempt long-term trials with lower doses of budesonide. Indeed, Renkema himself states, **"It may be that still higher doses of corticosteroids are needed in patients with COPD."** Renkema at page 1161, col. 2, second paragraph. This can be taken as a teaching-away from use of anything less than 1600 μg budesonide per day. As claims 27, 28, 33-47, 53, and 56-58 include doses of budesonide that are less than 1600 μg budesonide per day, one of ordinary skill in the art would not read Renkema to suggest that COPD can be treated with these amounts of budesonide with a reasonable expectation of success.

3. As further evidence of nonobviousness, Applicants' previous reply also reminded the Examiner of the surprisingly beneficial results achieved when patients with COPD were treated with the combination of formoterol and budesonide. The Examiner finds these arguments "unpersuasive" on the grounds that Carling *et al.* teaches "the same combination having same ratio for the greater efficiency result of treating respiratory disorder which includes COPD." Office Action at page 8. Since Carling *et al.* do not teach anything about COPD, this reference certainly could not have led one of ordinary skill to expect the remarkably good clinical results that were in fact produced by the claimed combination of drugs in patients with COPD.

The Examiner is also reminded that the court in In re Soni, 54 F.3d 746, 751 (Fed. Cir. 1995), stated that "when an applicant demonstrates *substantially* improved results...and *states* that the results were unexpected, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." (Emphasis in original). The Declaration of Dr. Jan Trofast submitted with the previous reply ("the Trofast Declaration"), and also the Declaration of Christer Hultquist submitted December 13, 2001, describe the unexpected results observed during treatment of COPD with the combination budesonide/formoterol therapy. The results presented in the Trofast Declaration supplement the data published in Calverley *et al.* (*Eur.*

Respir. J. 22:912-919, 2003). In an earlier Declaration by Jan Trofast, submitted March 1, 2004, Dr. Trofast described the results presented in Calverley *et al.* showing the effect of the combination of formoterol and budesonide to reduce the frequency of exacerbations as **"surprising given the low efficacy or ineffectiveness of treatment with either budesonide or formoterol alone."** March 1, 2004, Trofast Declaration at page 5.

As described above, the Examiner remains apparently unconvinced by Applicants' surprising results because she reads Carling *et al.* as teaching the same combination to treat asthma and "other respiratory disorders," and the Examiner reads "other respiratory disorders" as including COPD, because Giardina categorizes COPD as a respiratory disorder. The general term "respiratory disorders" as used in Carling *et al.*, combined with the fact that an unrelated reference (Giardina) lists a wide variety of conditions under the broad category of "respiratory disorders," does not qualify as "evidence to the contrary" under the standard of In re Soni. Unless the Examiner can provide genuine "evidence to the contrary," Applicants' evidence of unexpected results described in both Trofast declarations and the Hultquist declaration must be given due weight as cogent and persuasive evidence of nonobviousness.

4. In the previous reply, Applicants also noted that even years after the present application's filing date, experts in the field of respiratory therapy continued to express doubt that budesonide (whether alone or in the claimed combination therapy) would be useful for treating COPD. The Examiner states that this is not persuasive because, in her view, Carling teaches the combination therapy for treatment of respiratory disorders, and each of the active agents is allegedly taught by the cited references to be useful for the treatment of COPD.

MPEP 2141(III) explains that objective indicia including unexpected results and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these objective indicia is submitted, the Examiner must evaluate the evidence. The Examiner cannot dismiss Applicants' evidence of objective indicia of nonobviousness merely because she believes she has constructed a *prima facie* obviousness argument. The ultimate determination on patentability is made on the entire record. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Applicants maintain that when read in context, Carling *et al.* is understood not to encompass

treatment of COPD. This view is supported by the knowledge in the field at the filing date of the application. Furthermore, in view of Applicants' unexpected synergistic results observed with the combination therapy for treatment of COPD, and the skepticism of experts regarding the use of budesonide, Applicants maintain that one of ordinary skill in the art would not have read Carling *et al.* to teach a combination therapy for the treatment of COPD with a reasonable expectation of success.

In view of the foregoing, and the totality of the arguments in the record, Applicants request withdrawal of the rejection under 35 U.S.C. § 103.

Please apply the $450 fee for the Petition for Extension of Time for two months, the $500 fee for the Notice of Appeal and any other necessary charges or credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-150003.

Respectfully submitted,

Date: Nov. 15, 2006

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

DocNo 21478981